THE OXYTOCIC ACTION OF QUININE.[1]

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Since Petitjean,[2] in 1845, wrote that he had so often seen abortion produced during the administration of quinine for intermittent fever, that he no longer attempted to cure this disease during pregnancy, medical literature has teemed with discussions of the asserted oxytocic action of this drug. In 1855, Dr. John S. Wilson[3] described the uterine action produced by quinine, and in 1860, Dr. J. H. Rich[4] reported several cases of alarming uterine hemorrhage speedily checked by its means.

During the following year the oxytocic action of quinine was insisted upon by Cochran, Canada, Crouse, and Lewis;[5] Cochran asserting that the influence it exhibited in delicate, nervous, and irritable pregnant women predisposed to abortion. In 1871, Sayre[6] wrote to similar effect. General attention had not been attracted to this subject, however, until the appearance of an elaborate article by Monteverdi,[7] in the same year. This author declared that the special action of quinine upon the sympathetic system determined the contraction of those muscular fibres dependent upon it, particularly of the uterus, the intestines, the bladder, and the bloodvessels; that this contraction is physiological after small doses, but that after large doses a condition of constant tension results; that in a half hour after a moderate dose, brief contractions occur in the uterus, at first unaccompanied by pain, but gradually becoming stronger and longer with distinct intermissions, so as to resemble ordinary labor pains. This effect, he claimed, lasts about two hours and then subsides. Monteverdi concluded that quinine should be given with prudence to pregnant women, and that it is a trustworthy ecbolic and preferable to ergot.

This paper received at once widespread attention and provoked expressions of opinion from physicians everywhere, especially from those who practised in malarious districts. That quinine possesses positive oxytocic properties was asserted by a large number of writers in many and widely separated countries. Among these were Delioux de Sauvignac,[1] Duboué,[2] Hehle,[3] Pollak,[4] Josch,[5] Eaton,[6] Walraven,[7] Deneffe,[8] Rancillia,[9] Landis,[10] Wells,[11] Gray,[12] Packard,[13] Magnin[14] (who also quotes as confirmatory Cauterman, Horand, Danielli, Bianchi and others), and Wathen.[15] In a discussion before the St. Louis Medical and Surgical Society,[16] ecbolic properties were confidently ascribed to quinine by Drs. Hendrix, Burnett, Hurt, Morrison, Rowland, and Holland. Confirmatory observation was also made by Blackwood,[17] Benson,[18] Wiendahl,[19] Haussmann,[20] Paterson,[21] Roberts,[22] Powell,[23] Downes,[24] Burt,[25] Lewis,[26] Bardill,[27] Ghose,[28] Cayley,[29] Westmoreland,[30] Barrett,[31] Bracchi,[32] and Stewart.[33] While all of these writers agree as to the power of quinine to excite uterine contraction, they differ widely concerning the extent to which it possesses this property. They also discuss various directions in which the power may be exhibited; in the control of hemorrhage, simple or post-partum, in initiating the pains of abortion or of labor, in stimulating the force of contractions already established, and in facilitating the third stage of labor. Some claim that its abortifacient action is exerted only during the early months of pregnancy (Pollak, Haussmann); others, only toward its close (Ghose, Wiendahl). Bouqué (Magnin) asserts that it exerts a selective action upon the fibres of the body of the uterus, to the exclusion of the cervix, while Chirone[1] and Sacchi[2] consider it most effective in promoting dilatation.

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[1] Read before the Clinical Society of Maryland, October 4, 1889.

[2] Gaz. des Hôpitaux, Ranking's Abstract, vol. i., 1845.

[3] Southern Medical and Surgical Journal, 1855, 341.

[4] Charleston Med. Journ. and Review, March, 1860.

[5] Cincinnati Lancet and Observer, July, 1861; also, Hamilton, ibid., July, 1861.

[6] American Practitioner, 1871.

[7] Bull. de la Soc. de Méd. de Gand, vol. xxxviii. p. 239, 1871. American Journal of the Medical Sciences, lxii., 1871.

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[1] Bull. Général de Thérapeut., 1871, lxxxi. p. 298.

[2] L'Union Médicale, 1871, xii. 545.

[3] Wiener med. Presse, 1871, 36, and 1822, 29.

[4] Ibid., 1872, 13. 708.

[5] Ibid., 1872, 13.

[6] Kansas City Medical Journal, April, 1872.

[7] Gaz. Obstetricale de Paris, 3, 1873. 350.

[8] Boston Medical and Surgical Journal, 1873.

[9] L'Union Médicale, 1873.

[10] Philadelphia Medical Times, vol. iii. 276.

[11] Louisville Medical and Surgical Journal, July, 1874.

[12] Obstetrical Journal of Great Britain, i., 1873, 398.

[13] Ibid., ii., 1874, 446.

[14] Thèse de Montpelier, No. 64, 1873.

[15] Practitioner, xvii., 1876, 38.

[16] St. Louis Medical and Surgical Journal, xlv. 159.

[17] Medical and Surgical Reporter, January, 1875.

[18] Practitioner, vol. xxiii., 1879, 428.

[19] New Orleans Medical and Surgical Journal, December, 1885.

[20] Berliner klinische Wochenschr., 1882, 562.

[21] Practitioner, July, 1877.

[22] Ibid., vol. xviii. 256.

[23] Medical Brief, ix., 1881, 135.

[24] Lancet, ii., 1880, 616.

[25] Medical and Surgical Reporter, February 5, 1870.

[26] Ibid., 1870.

[27] Rocky Mountain Medical Review, December, 1880.

[28] Indian Medical Gazette, 1882, p. 141.

[29] Ibid.

[30] Atlanta Medical and Surgical Journal, xvi., 1878-79.

[31] St. Louis Medical and Surgical Journal, xlv., 1883, p. 160.

[32] Raccoglitore Med. Forli, xxiv., 1885, 275.

[33] Medical and Surgical Reporter, lviii., 1888, 13.

All these observers, agreeing in their main facts, find some confirmation of their opinions in a more or less widespread popular prejudice against the use of quinine during pregnancy. Monteverdi was induced to study the subject by finding this prejudice prevalent among the women of Cremona, and Roberts asserts that in India all the natives attribute ecbolic action to the drug, while Paterson states that this opinion is held not only by the natives of India, but by those all over the East.

But the number and credibility of the observers cited is almost, if not quite, equalled by those who absolutely deny that quinine has any properties of stimulating uterine muscular fibres. Already in 1846, Rodriguez[3] denied Petitjean's assertion that it is dangerous to give quinine to pregnant women, and related fifteen cases of intermittent fever during pregnancy which he had treated with quinine with no unpleasant result, and in 1858, Dr. Joseph W. West[4] declared that the drug had no abortifacient power. Subsequently, similar conclusions were drawn by a very large number of writers, most of whom, living in malarious districts, had excellent opportunities to make their observations and who had been in the habit of employing quinine in the treatment of malarial fevers during pregnancy, freely and without fear. Among these are to be mentioned Beauchamp,[5] Rooker,[6] May,[7] Russwurm,[8] Bailey,[9] Bordley,[10] Brown,[11] Erickson,[12] Harris,[13] Rutland,[14] Seads,[15] Ashford,[16] Lee,[17] d'Arcourd,[18] Erwin,[19] Plumb,[20] Lincoln,[21] Bergele,[22] Brochin,[23] Prunac,[24] Tissus,[25] Taillard,[26] Senre,[27] Vicali,[28] Lewis,[29] Campbell,[30] Watkins,[31]

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[1] Lo Sperimentale, 1875 (Virchow und Hirsch, Jahresberichte für 1875).

[2] Revista Med. di Bologna (Virchow und Hirsch, Jahresberichte für 1875).

[3] Ranking's Abstract, vol. iv. p. 311.

[4] Savannah Journal of Medicine, vol. i. 19.

[5] American Practitioner, 1870.

[6] Ibid., 1870.

[7] Ibid., 1870.

[8] Ibid., 1871.

[9] Medical and Surgical Reporter, 1872.

[10] AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 64, 1872, 287.

[11] Ibid., 64, 1872.

[12] Ibid., 64, 1872.

[13] Ibid., 64, 1872.

[14] Ibid., 64, 1872.

[15] Ibid., 64, 1872.

[16] Ibid., 63, 1872.

[17] Ibid., 63, 1872.

[18] Medical News and Library, May, 1873.

[19] St. Louis Medical and Surgical Journal, March, 1873.

[20] AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 66, 1873.

[21] Ibid., 66, 1873.

[22] Wiener med. Presse, 1872.

[23] Gazette des Hôpitaux, 1875.

[24] Ibid., 1875.

[25] Ibid., 1875, p. 20.

[26] Ibid., 1875, p. 43.

[27] Ibid., 1875, p. 379.

[28] Ibid., 1875, p. 1107.

[29] Virginia Med. Monthly, Feb. 1878.

[30] American Journal of Obstetrics, 1880.

[31] St. Louis Medical and Surgical Journal, xlv. p. 159.

Henry,[1] Wood,[2] J. D. Smith,[3] Payne,[4] Cullen,[5] Ahmed,[6] Chiari,[7] and Bazin.[8] Many of these writers derived their experience from years of practice and abundant opportunities for observation. Ahmed, for example, did not remember a single abortion produced by quinine in a dispensary service at Burdwan (during epidemics of 1871–72–73) with an attendance of 300 or 400 patients daily, at which hundreds of pregnant women were treated and where a pound of quinine was dispensed daily. They did not deny that abortion and premature labor often occur during the course of malarial fevers, but it was claimed that this result is due to the fever and not to the quinine; that, indeed, the best measure to prevent the abortion is the timely and sufficient administration of this remedy. Illustrative cases were brought forward in abundance.

That abortion and premature labor are not uncommon during malarial fevers is widely admitted. Definite proof of this, however, is by no means readily obtainable; statistics are largely wanting. The figures of Góth[9] relating to this point are very interesting. This writer states that in a lying-in hospital in a highly malarious district, there were (during a period of six years, 1873–78) 881 women delivered; of these, 46 were affected with malaria during a longer or shorter portion of their pregnancies. In 27 of these pregnancy reached its full term. Abortion or premature labor occurred in 19. Thus, pregnancy was interrupted in 41.3 per cent. of the malarial patients. Góth also shows that the large majority of these premature labors occurred during the seventh and eighth months. But since in institutions it is not usual for patients to be admitted earlier than this period, these figures are probably without value. Unfortunately, Góth's observations seem to have had no reference to the concurrent administration of quinine, though he incidentally refers to the powerlessness of the agent to prevent labor in certain cases, and they are open to the objection that they do not place beyond suspicion a possible abortifacient influence of this agent. The universal use of the alkaloids of Peruvian bark in the treatment of malarial disorders renders a study of the abortifacient tendencies of malarial intoxication extremely difficult. It is most important that such should be made. Certainly, several of the writers already cited found that pregnant women who aborted while suffering from malarial fever for which they were taking quinine, passed through later pregnancies to full term, though experiencing attacks of malarial fever repeatedly, but from whom quinine had been withheld.

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[1] Ibid., xlv. p. 83.

[2] Phila. Medical Times, 1874, p. 143.

[3] Mississippi Valley Medical Journal, vi., 1886, p. 450.

[4] Gaillard's Medical Journal, xxxiv. 315.

[5] Indian Medical Gazette, October 1, 1881.

[6] Ibid., 1882, ii. p. 165.

[7] L'Union Médicale, xvi., 1873.

[8] Ibid., xvi., 1873.

[9] Zeitschrift für Geburtshülfe u. Gynäkolog., 6, 1881, 17.

Whatever be the result of individual investigations, they cannot negative the conclusion, which the observations of a large number of competent reporters seem to justify, that quinine excites no definite pharmacological or physiological contractions in the uterine musculature, especially during pregnancy. It is in the highest degree improbable that, had this agent this property as part of its regular physiological action, numbers of competent observers, practising in highly malarious localities and giving the drug fearlessly in large and repeated doses to pregnant women, should have failed to notice it. This negative evidence has seemed sufficient to cause a rejection of the claims of quinine to oxytocic action in the text-books. Many of the authors do not even deem the subject worthy of notice. Horatio C. Wood,[1] however, has most carefully considered the whole question, and in an excellent *résumé* gives in detail the reasons for his adverse opinion.

While, however, we may deny that quinine has this definite and fixed physiological property, are we equally prepared to deny that it may produce this effect as part of an irregular and unusual operation? Agreeing that it has no claim to be held as a fixed oxytocic remedy, we must have recourse to idiosyncrasy to reconcile the statements of the numerically large but relatively small number of physicians who have observed its oxytocic effects with the negative testimony of many whose experience has been as large and whose credibility is as great.

Leaving out of consideration the often-asserted hæmostatic properties of quinine—properties that have been claimed for it by many writers (Rosenstein, Hoffmann, Wagner, Vogel, Morton, and others for general hemorrhages, and Deboué, Melchior, Rabot, Gerelli, Barthouz, Deneffe, Guéneau de Mussy, and many others for uterine hemorrhage)—I propose to submit a few cases, selected from a large number upon record, in which it is difficult to avoid the conclusion that a specific action was exerted by quinine upon the uterine musculature. From this consideration have been rejected the large number of reports concerning the action of the drug in promoting the pains of labor already established, as being too liable to erroneous interpretation. It is very unfortunate that observations of the effects of quinine upon pregnant animals have been very few. Such as they are, they do not show constant results. Three of them seem to be of sufficient importance to merit a brief notice. Two of these were made by Rancillia, and one by Magnin. They were as follows:

EXPERIMENT 1.—A spaniel bitch had been covered eighty days previously, and was consequently fifteen days overdue. She was depressed, without appetite, and had a muco-purulent discharge from the vulva.

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[1] Therapeutics, Materia Medica, and Toxicology, 2d edition, 1877, p. 61.

Four grains of ergot were given her morning, noon, and night, but without effect. Two days later, Rancillia administered three-quarters of a grain of sulphate of quinine every half-hour. After the eighth dose violent contractions began. These resulted in the expulsion of three dead and partly decomposed pups.

EXPERIMENT 2.—A little bull bitch had been covered accidentally by a strong Newfoundland dog, forty-nine days previously. She had become so big as to excite in her owner fears for her safety. Rancillia gave her one and a half grains of sulphate of quinine every half-hour. At the sixth dose she was delivered of six living pups.

EXPERIMENT 3 (Magnin).—This was upon a doe rabbit, which had been covered twenty-four or twenty-five days previously. August 4th Magnin injected three-quarters of a grain of sulphate of quinine at 8.30 o'clock A.M. At 8.35 o'clock a second injection of three-quarters of a grain was given. These injections were repeated every fifteen minutes for two hours. At 10.30 o'clock the experiment was suspended. The rabbit was then very restless and had a hot skin. At 2 o'clock P.M. she seemed very well, having eaten during the interval. Injections of three-quarters of a grain were resumed, but at intervals of ten minutes. Of these she had two, and at 3.45 o'clock three young rabbits were found dead by her side.

In two other experiments made by Magnin abortion did not occur. In one, the animal died without aborting after 11½ grains had been injected. The necropsy revealed great distention of the stomach, with congestion of the intestines, uterus, and brain. The experiments of H. C. Wood resulted negatively. This observer gave quinine to two pregnant cats, "in one case in sufficient quantity to cause death without disturbing the products of conception." Chirone has also noted the possibility of death following the administration of quinine to pregnant animals without having been preceded by abortion.

These experiments are too few to justify positive conclusions, but they seem to show that the uterine muscular fibres of animals may occasionally be stimulated to activity by quinine. Passing to the human subject, it can be shown, in the first place, that quinine may excite uterine pains in pregnant women without precipitating labor. This has been attested by various writers, but one or two examples will be enough for our purpose.

CASE I. (Haussmann[1].)—Frau X., during the autumn of 1881 had neuralgia of the right tibial nerve. This began at 3 o'clock P.M., and lasted until night. Large doses of quinine were given, but without result, and the neuralgia only ceased upon her return to her home. Since March 1, 1882, this neuralgia had returned regularly at 3 P.M. March 14th, she was given 15 grains of sulphate of quinine at one dose, upon an empty stomach. The neuralgia was but slight the succeeding evening. Next day (15th) the dose was repeated at one o'clock. Early on the 16th she had slight pain in the toes, but she took no quinine this day. March 17th, she took 15 grains of sulphate of quinine in four doses. She now took no more until March 24th, when, the neuralgia having recurred with constantly increasing intensity, 15 grains were given, and this dose was repeated the next day. The attacks became feebler, but did not quite cease. March 28th, she had 23 grains of sulphate of quinine, after which the attacks did not return. This naturally strongly-built woman had aborted about a year and a half previously. Early during the preceding year she had only been saved from a second mishap by opium. She had again conceived in January of the current year (1882). For the first two days of the administration of quinine, which was during the latter part of the third month of pregnancy, she experienced, about two hours after its ingestion and almost simultaneously with the beginning of the *tinnitus aurium*, severe pains of precisely the same character as she had had in her first, completed, and her second threatened, abortion. The uterine contractions lasted at least two hours, and on the first days caused a slight show of blood from the genitalia. They finally ceased spontaneously under rest. On the following days the pains began from four to six hours after the ingestion of the quinine, and were briefer; except on March 28th, when there was a very slight loss of blood. Finally, on March 29th, when 23 grains of sulphate of quinine were taken upon an empty stomach, the pains began almost as soon as it was swallowed, although vomiting occurred about one and a half hours later, and continued with the pains until evening, when the latter again disappeared spontaneously. *On the other hand, on those days, and especially the afternoons, when no quinine was given (March 18–23), there were no pains.* Haussmann attributed this unusual effect of quinine to a greatly debilitated, anæmic, and wasted condition in a woman in whom there was an undue irritability of the uterine system, and concluded that only from inordinate doses or in debilitated conditions are oxytocic effects to be feared.

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[1] Berliner klin. Wochenschr., No. 37, 1882, 566.

Case II. (Deboué.[2])—Every time this patient, a pregnant woman, took quinine (from 9 to 12 grains daily) she experienced, for a quarter or half an hour, pains in the lower portion of the abdomen, apparently situated in the uterus and accompanied, especially during the first days, by true contractions of this organ. As the young woman regained her health the contractions had less and less energy and duration. Two years later (December, 1868) this same woman had a return of remittent fever during pregnancy and Deboué gave her 22 grains of sulphate of quinine daily. He noted very distinctly the development of uterine contractions at each dose. Deboué had seen other similar cases, but did not think that doses of from 12 to 15 grains daily were sufficient to produce abortion.

Case III. (Burt.[1])—The mother of five children was in her sixth pregnancy. Burt was called to attend her in September, 1869. She then had intermittent fever and was four months pregnant. A chill was expected in a few hours and Burt gave her eight grains of quinine sulphate and left her to visit another patient. Upon his return she told him that she was in labor, the pains being regular and seemingly natural. She was quickly brought under the influence of morphine, when the pains gradually left her. She had had no return of them when last seen, four months later, although she had suffered from intermittent fever repeatedly.

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[1] Medical and Surgical Reporter, Feb. 5, 1870, p. 120.

[2] L'Union Médicale, xii., 1871, p. 545.

CASE IV. (Barret.[1])—"I gave the quinine several times and labor pains were produced, and then I stopped and the pains subsided; and then I gave the quinine again and the pains reappeared."

CASE V. (Danielli.[2])—A woman, twenty-eight years old, had had five labors and one abortion at five months. She was pregnant for the seventh time. In the middle of June she had enteritis and quotidian intermittent fever. She was ordered to take 12 grains of sulphate of quinine daily, but this had to be discontinued on account of the uterine pains it excited. Under a renewed administration of the remedy these pains reappeared. Toward the end of June the fever reappeared and another physician was called to attend her. She was again given sulphate of quinine, which was again followed by intense uterine pains, and, this time, by abortion.

CASE VI. (Wathen.[3])—A weakly, delicate woman came under treatment (April 18th) for severe neuralgic pains extending over the whole of one side. There was slight pyrexia, but no physical signs of disease were detected. After expressing the opinion that the case was one of an epidemic class of pleuro-pneumonia that was prevailing in the neighborhood at the time, the writer proceeds: "On the 21st (salines having been given until then), two grains" (of quinine) "were ordered to be given every four hours. The case, apparently doing well, was not seen for several days, when the patient stated that after taking a few doses of quinine, strong bearing-down pains came on—'worse than any labor pains she had ever had'—and, after nearly a whole day of pain, to her astonishment, a good-sized mass was expelled from the uterus." This was a tumor of the size and shape of an ordinary-sized bun. It had all the characteristics of a fibroid. There was no pedicle, and Wathen thought it most probably intra-mural. The patient stated that there had been no menorrhagia and that she had not experienced any uncomfortable feeling to indicate that there was anything wrong with the womb.

CASE VII. (Hehle.[4])—The patient was a multipara, thirty-two years old, very anæmic and debilitated. She had complained for four months of repeated irregular uterine hemorrhage. The uterus was felt as an oval body, the size of a fist, above the *symphysis pubis*. The uterine contents could not be defined upon vaginal examination on account of the high and narrow cervix. During the succeeding two months Hehle succeeded, by various therapeutic measures, in preventing large hemorrhage, but there continued constant oozing and the patient became increasingly debilitated. Having determined to empty the uterus of its contents, he ordered twelve grains of sulphate of quinine to be taken at five o'clock A.M., and three grains every second hour thereafter. After the last dose, at eight o'clock P.M., pains began and continued throughout the night and the two following days. Being summoned on account of the pains, Hehle found the os dilated to the size of a thaler, the cervix effaced and the uterine cavity containing a dense tolerably elastic body. Failing to dislodge this mass with his finger, Hehle now gave ergot and the mass was soon extruded. It was a hydatid mole weighing about one pound.

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[1] St. Louis Med. and Surg. Journ., xlv., 1883, p. 160.

[2] Quoted by Magnin.

[3] Practitioner, xvii., 1876, p. 38.

[4] Wiener med. Presse, No. 36, 1871, p. 911.

A very bulky amount of evidence has been recorded to show that abortion or premature labor has been brought about by quinine directly. It is nearly always difficult, however, to assign definitely to a drug an influence in producing untoward results in the course of diseases which are known to be capable of producing them, occasionally, of themselves. Thus, in those maladies in the treatment of which quinine is usually most freely employed, *e. g.*, malarial fevers, pneumonia, typhoid fever, etc., pregnant women often enough abort simply from the effects of the specific morbid action; and while the relation of cause to effect may often be determined to the satisfaction of those whose opportunities have permitted a personal observation of the phenomena, the connection is by no means so clear to those whose knowledge must come at second-hand. In this manner, much of the evidence upon this subject has failed to satisfy the critical reader; and possibly, on the other hand, it is thus that the prejudice of an observer may cause him to reject evidence tending to prove the potency of the drug, in favor of that of the disease, in determining the result. Many of the reports make it not at all clear that the result has been due to the drug rather than to the disease, and this obscurity is very often attributable to careless or imperfect observation. There are many, however, in which the proofs seem to be fairly credible. Of this considerable number, a few examples only are here appended.

CASE VIII. (Bianchi.[1])—A woman, forty-three years old, had had six children at full term. In 1868 she conceived a seventh time. Toward the end of the fifth month she was attacked with intermittent fever, which was accompanied by violent dyspnœa. She was given for this, sulphate of quinine, but this agent provoked uterine pains with violent hemorrhage. Two children were born and the woman made a good recovery. In 1869 she became pregnant for the eighth time. During the eighth month she was seized with orthopnœa and cardialgia. Sulphate of quinine and digitalis were given. Labor began shortly afterward. It was quickly accomplished and she again made a good recovery. This woman now passed three years in perfect health, but toward the middle of March, 1872, when six months pregnant, she was again threatened with orthopnœa and cardialgia, though auscultation and percussion revealed nothing abnormal. The symptoms were so grave that asphyxia appeared imminent. There was albuminuria with œdema of the lower extremities. With a view of evoking labor pains, Bianchi now prescribed the sulphate of quinine. He ordered a pill of 4 grains to be taken every half-hour. After she had taken five of these pills (20 grains), lumbar pains were developed. After a sixth pill the uterine contractions became regular, the cervix softened and the os dilated. Toward midnight, however, the pains ceased and the orthopnœa became so distressing that B. thought of turning and delivering. Before doing so, however, he administered another dose of quinine. In less than a half-hour the uterine contractions and the pains reappeared and the accouchement terminated happily.

[1] Quoted by Magnin.

CASE IX. (Downes.[1])—A lady expected her confinement at the latter part of August. In the middle of July she had fever, which, at first of an intermittent kind, showed a tendency to become continuous. Downes endeavored, with some success at first, to stay the fever with jaborandi and arseniate of quinine, without giving sulphate of quinine. The amount of quinine in the arseniate was so small that he did not hesitate to give it. Nearly a month passed and the fever was so bad and intractable and the patient became so weak that he began to fear the consequences, both to mother and child. Therefore, on August 7th, he began to give the sulphate of quinine in five-grain doses, three times daily. She took one dose in the morning and one at midday. At about 8 o'clock in the evening, without warning, the waters broke and slight uterine pains came on. The child was delivered at 11 o'clock. It was very small and looked as though it had been born a month before its time.

CASES X., XI., XII. (Blackwood.[1])—The first patient was in the eighth month of her pregnancy when she was attacked by a quotidian intermittent fever. She took three grains of sulphate of quinine every fourth hour for three days. As there was no decided improvement, on the fourth day she took five grains every fourth hour. After she had taken twenty grains, labor pains began and delivery was completed. The second patient was in the seventh month of a fifth pregnancy. She was seized with quotidian intermittent fever. She was given three grains ot sulphate of quinine every fourth hour. After this treatment had been continued four days, labor set in and was completed. The third patient was seven months pregnant. She also was seized with quotidian intermittent fever. Labor began after she had taken thirty grains of sulphate of quinine. All three of these women had previously been healthy and had never miscarried. *Within the two succeeding years Blackwood was called to attend each of these women for intermittent fever while they were pregnant. He now treated them with arsenic and in neither was pregnancy interrupted.*

CASE XIII. (Personal.)—On January 18, 1889, I was summoned to attend Mrs. D., who was in the eighth month of her first pregnancy. She was a small but perfectly healthy-looking woman, and had been well up to the day previous. During the autumn she had been in the country with her husband. She had never previously had malarial fever, but upon the date of my visit had had a chill followed by fever, which was passing off when I saw her. No specific treatment was ordered. On the 19th she had another chill and fever, and on the 20th the paroxysm was repeated. A quotidian intermittent fever was diagnosticated and the importance of controlling the attacks was urged upon the family, and at the same time the asserted oxytocic action of quinine was explained, with, however, some expression of incredulity. The decision being left with me, I ordered five-grain doses of sulphate of quinine, in capsules, every fourth hour until twenty-five grains had been given during twenty-four hours. The remedy was given too late on the 20th to interfere with the paroxysm and although the full amount was taken and retained, the paroxysm appeared to be in no manner influenced on the 21st. Twenty-five grains were again administered during the day as before, and on the 22d there was no paroxysm. Though there had been no fever since the afternoon of the 21st, upon my visit on the morning of the 22d my patient told me that she had since early morning transitory lumbar pains. These increased during the evening and night, and on the morning of the 23d I found her in labor. Her child, born just before midnight, was a tiny creature with a thick down of lanugo hairs over its forehead, temples, cheeks and body, and seemed considerably younger than an infant at term. It was living, however, and lived. The mother made a good recovery and had no return of the malarial fever. During the paroxysms the temperature did not exceed 103.5° F.

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[1] Lancet, ii., 1880, 616.

[2] Medical and Surgical Reporter, January 9, 1875, 23.

The foregoing cases are a few of the many observations made by nearly a hundred physicians during the last forty years in many parts of the world. They all lack the scientific accuracy of a mathematical demonstration, since in every observation, upon the human subject at least, the action of the remedy was liable to be confounded with that of the disease upon the organism. An unprejudiced criticism of many reports leaves one unable to decide the value of the testimony; but in many others it is difficult not to recognize the action of quinine upon the uterine musculature. There is no difficulty in determining such action to be inconstant. Indeed, a number of writers have shown that quinine not unfrequently prevents abortion by its power of counteracting abortifacient morbid action. It is significant that many of those who deny that quinine ever acts as an oxytocic, freely admit that malaria itself may provoke uterine contractions and interrupt pregnancy. It is extremely improbable that any malarial patients escape the ingestion of quinine, unless by accident, and it is thus that a certain number of the cases supposed to illustrate the abortifacient tendencies of malarial intoxication, may, in fact, present examples of idiosyncratic reaction to the presence of quinine in the system. The latter possibility, supported by the observations of the large number of writers already quoted, certainly justifies the demand for renewed attention to the subject.

In conclusion, the following propositions are submitted:

1. The cinchona preparations have not a fixed and definite influence in causing contractions of the uterus.

2. An oxytocic action is occasionally produced by these remedies. This action depends upon idiosyncrasy; and, as in the other idiosyncratic reactions to cinchona, it is impossible to foretell, in any given subject, its manifestation.

3. There is some evidence that this action is only exerted under large doses or in debilitated subjects.

4. Cinchona and its derivatives should be employed during pregnancy with great circumspection and should be at once withheld upon the supervention of symptoms indicating a uterine-motor influence.